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References: 1. Indust. Med 22:311 (July) 1953. 2. Journal-Lancet 76:190 (July) 1956. 3. J. Chronic Dis. 2:645 (Dec.) 1955.

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STUDIES ON THE PATHOGENESIS OF FEVER.

VI. The Effect of Heat on Endogenous and Exogenous Pyrogen in the Serum of Dogs[1]

ROBERT G. PETERSDORF[2] AND IVAN L. BENNETT, JR.

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Received for publication December 20, 1956

Intravenous administration of typhoid vaccine to rabbits is followed by the appearance in the serum of two separate pyrogens (1, 2). The first is present in highest concentration during the few minutes immediately after the administration of vaccine, is rapidly cleared from the circulation, and is thought to be identical with the initially injected exogeneous bacterial pyrogen. The second is present in serum 60–120 minutes after injection of vaccine and has been postulated to be of endogenous origin. These substances differ in two respects: (a) in normal rabbits the temperature response to each is distinctive; (b) only the later pyrogen produces fever in animals "tolerant" to bacterial endotoxin.

Recent investigations in this laboratory have demonstrated a late appearing pyrogen (henceforth called "endogenous" pyrogen) in the serum of dogs given bacterial endotoxins derived from *Salmonella*, *Shigella*, *Achromobacter* species, and *Escherichia coli* (3). The canine endogenous pyrogen is similar in its biological properties to that derived from rabbits. On the other hand, the early, rapidly-cleared serum pyrogen, which is easily and consistently detectable in the rabbit has not been found in the dog. This is presumably due to dilution and rapid clearance in this animal.

It has been postulated that endogenous serum pyrogen is a product of injured cells, perhaps polymorphonuclear leukocytes. In both the rabbit (4) and the dog (3), the intravenous injection of leukocyte extracts or acute sterile exudates is followed by a characteristic febrile response which is readily distinguishable from endotoxin fever. Because the biological characteristics of endogenous serum pyrogen and leukocyte extracts have been thought to be similar (see Table I), a study was undertaken to investigate and compare some properties of these two fever-producing substances as well as bacterial endotoxins.

Bacterial endotoxins are heat-stable, and the leukocyte pyrogen is rapidly destroyed by heat. It seemed pertinent, therefore, to investigate the effect of normal serum upon the heat-stability of bacterial endotoxins.

The present report describes a series of experiments in which canine endoge-

[1] This study was supported by Grant A-660 of the National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service.

[2] Fellow of the National Foundation for Infantile Paralysis.

TABLE I

*Biological Properties of Serum and Tissue Pyrogens**

	Bacterial Endotoxin (5 minute serum pyrogen)	Endogenous Serum Pyrogen (120 minute serum)	Leukocyte Pyrogen (Peritoneal exudates)
Temperature curve	Biphasic (6)	Monophasic (3)	Monophasic (4)
Destroyed by heat at 90°C.	No (6)	?	Yes (4)
Capable of inducing tolerance	Yes (5)	No (3)	No (8)
Shwartzman phenomenon	Yes (11)	Not done	No (3)
Response potentiated by RE blockade	Yes (12)	No (3)	No (8)
Fever in tolerant animals	No (2)	Yes (2)	Yes (8)

* Numbers in parentheses indicate references.

nous serum pyrogen was found to resemble leukocyte pyrogen closely in its susceptibility to heat. However, it was also found that the resistance of typhoid vaccine and other bacterial endotoxins to heating is frequently so reduced in the presence of normal serum that these "exogenous" pyrogens can not be distinguished from the "endogenous" substance on the basis of this property alone.

MATERIALS AND METHODS

Bacterial Endotoxins. The following vaccines and purified bacterial endotoxins were used: a formalin-killed *E. coli* vaccine containing approximately 8×10^6 cells/ml.; a heat-killed *E. coli* vaccine preserved with 0.5 per cent phenol containing 2×10^9 cells/ml.; a monovalent typhoid vaccine[3] (Army reference standard NRV-LS #1 prepared from *Salmonella typhosa*, strain V-58), containing 500×10^6 cells/ml.; a monovalent typhoid vaccine prepared from the Felix-Ty2 strain of *S. typhosa*[4], containing 6×10^9 cells/ml.; and purified lipopolysaccharide, ("Pyrexal") prepared from *Salmonella abortus equi* (lot AE 1298S4).[5]

Animals. Male and female mongrel dogs weighing 6–12 Kilograms were used in all experiments.

Preparation of Endogenous Pyrogen. Groups of "donor" dogs were given intravenous injections of 20 ml. of formalinized *E. coli* vaccine, 5.0 ml. of V-58 typhoid vaccine or 10 microgm. of Pyrexal and bled by cardiac puncture 120 minutes after administration of endotoxin. Blood obtained from each animal was allowed to stand at room temperature for one hour, and at 4°C. for an additional 24 hours. The serum was separated by centrifugation and stored at 4°C. All sera were used within one week after collection and there was no pooling from different donors.

Preparation of Endotoxin-Serum Mixtures. Serum was obtained from normal dogs by exsanguination and stored at 4°C. Endotoxin was added 30 minutes prior to injection into recipient animals and the mixture allowed to remain at room temperature.

[3] Kindly supplied by Col. A. S. Benenson, of the Army Medical Service Graduate School, Walter Reed Medical Center, Washington, D. C.

[4] Obtained from Dr. Maurice Landy, United States Public Health Service, Bethesda, Maryland.

[5] Made available by Dr. Otto Westphal, Dr. A. Wander Forschungsinstitut, Sankingen/Baden, Germany.

Preparation of Heated Serum. In order to prevent coagulation, an equal volume of distilled water was added to each serum sample prior to heating. (The addition of normal saline or smaller than equal volumes of water failed to prevent heat-coagulation). Serum samples were heated in a water bath at 60°C. or 90°C. for 30 minutes.

Recording of Temperatures. All temperatures were taken rectally for two minutes with clinical thermometers. Animals remained unrestrained within cages throughout each experiment; food and water were withheld. After baseline readings had shown an animal to be stable for 90 minutes, the material to be tested was injected into a leg vein and temperatures recorded at 30 minute intervals for four hours. Fever curves were graphed and the areas beneath them measured with a planimeter (Keuffel-Esser 4236M-9788) to obtain a "fever index" (5).

Miscellaneous. All needles and glassware were sterilized in hot air ovens at 170°C. for three hours; distilled water and 0.85 per cent NaCl solution were tested by injection into rabbits and demonstrated to be pyrogen-free before use. Samples of normal dog serum were shown to cause no fever in recipient dogs. All sera were cultured in thioglycollate broth and found to be free of bacterial contaminants.

RESULTS

The Effect of Heat on Endogenous Serum Pyrogen

A. *Pyrexal Serum.* Donor animals were given an intravenous injection of 10 microgm. of pyrexal and serum containing "endogenous" pyrogen was collected 2 hours later. Each of six recipient dogs (nos. 1–6) received a series of three injections of serum obtained from a single donor, prepared as follows: 10 ml. of

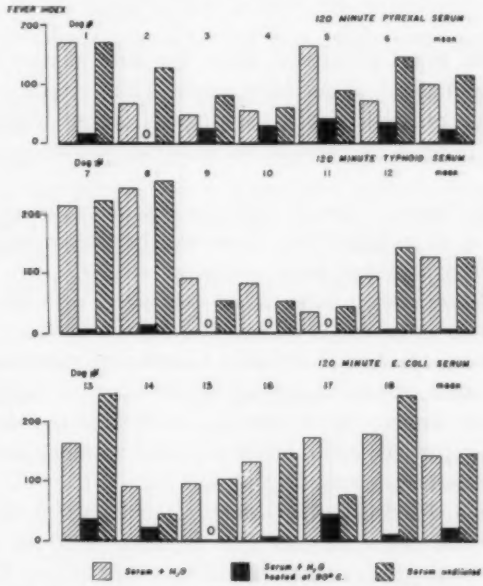

FIG. 1. Febrile response of 3 groups of dogs to unheated and heated endogenous pyrogen derived by administration of pyrexal, typhoid vaccine, and *E. coli* vaccine.

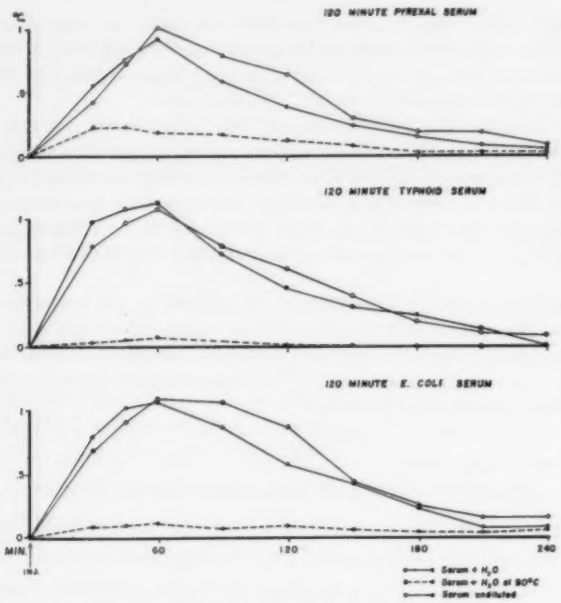

FIG. 2. Mean fever curves of 3 groups of dogs given diluted, undiluted and heated endogenous pyrogen.

serum mixed with 10 ml. of distilled water, the same mixture heated at 90°C. for 30 minutes, and 10 ml. of undiluted serum. Test animals were rested for at least 2 weeks after each injection to avoid complications of pyrogen tolerance. In addition, the order of injection of test materials was varied in "criss-cross" fashion.

As is shown in Figures 1 and 2, both the serum and serum-water mixture produced fever in all recipient dogs. However, heating serum-water mixtures at 90°C. completely abolished their pyrogenic activity.

B. *Typhoid Serum.* Donor animals for this group were bled 2 hours after having received an intravenous injection of 5.0 ml. typhoid vaccine (Army V-58). Recipient animals (nos. 7–12) were treated with serum and serum water mixtures in the same manner described for the previous experiment. The results were entirely similar. Again, heating inactivated the thermogenicity of endogenous serum pyrogen and dilution of serum with distilled water did not change the magnitude of fevers. (Figs. 1 and 2).

C. *E. coli Serum.* Six dogs (13–18) were injected with 10 ml. of 120 minute serum collected from donor animals after injection of 20 ml. of formalinized *E. coli* vaccine. Testing was carried out as described above. The results were similar to those with endogenous pyrogen obtained after both pyrexal and

typhoid vaccine although febrile responses to unheated serum were greater than in the preceding groups. (Figs. 1 and 2).

These data clearly demonstrate that endogenous serum pyrogens produced in response to different bacterial products are inactivated by heating at 90°C. for 30 minutes.

D. *Effect of Variation in Temperature.* A pool of serum containing endogenous pyrogen which had been shown previously to be inactivated at 90°C., was diluted with an equal volume of distilled water and one-half of the mixture was then heated at 60°C. for 30 minutes. Twenty ml. aliquots of the heated and unheated mixture were then tested in a group of six normal dogs (nos. 38–43).

The procedure resulted in no change in the ability of the serum to produce fever. The mean fever indices were 109 for the unheated material and 120 for the serum heated at 60°C. Table II details the results in individual animals. In other experiments, it was shown that exposure of endogenous serum pyrogen to 37°C. for periods up to 12 hours does not diminish its pyrogenic activity (3).

The Effect of Heat on Bacterial Endotoxin Added to Serum

Pyrexal. One microgm. of the endotoxin added to 10 ml. of normal canine serum and 10 ml. of water was injected into each of six animals (nos. 19–24) in the unheated state and after heating at 90°C. for 30 minutes. These recipients were tested in criss-cross fashion, and at least 2 weeks were permitted to elapse between injections.

Heating the pyrogen-serum-water mixture, completely abolished its capacity to produce fever in five animals, and markedly diminished it in the sixth (Figs. 3–4). When 1.0 microgm. of pyrexal in distilled water was heated at 90°C. *without* the addition of serum, it produced a febrile response in each of a group of six normal dogs, the indices ranging from 65 to 185 with a mean of 116.

Typhoid Vaccine. A mixture of 1.0 ml. of typhoid vaccine (Army V-58), 10 ml. of normal serum and 10 ml. of distilled water was also pyrogenic for six

TABLE II

The Effect of Heating at 60°C. on Pyrogenicity of Endogenous Serum Pyrogen

Recipient Dog No.	Fever Index Unheated	Fever Index 60°C.
38	159	198
39	36	32
40	130	126
41	144	77
42	107	194
43	76	90
Mean	109	120

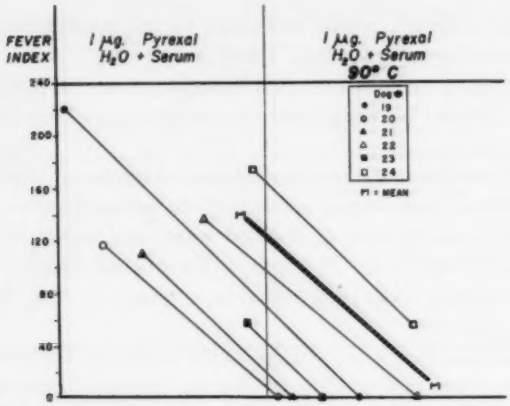

FIG. 3. The effect of heating on the thermogenicity of a pyrexal-serum-water mixture in 6 dogs.

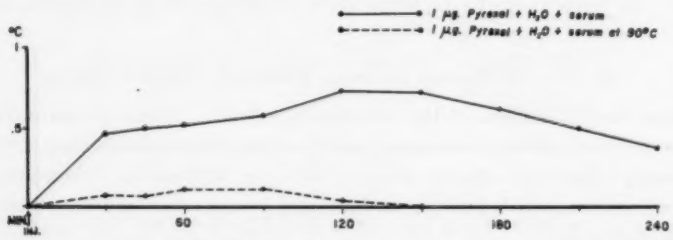

FIG. 4. Temperature records of 6 dogs illustrating the inactivation of pyrexal in the presence of serum and heat.

dogs (nos. 25–30). This mixture of pyrogen and serum produced no fever after it had been heated at 90°C. for 30 minutes. (Figs. 5A, 5B, 6). These results contrast sharply with the reported heat-stability of bacterial endotoxins (6) and occurred only when serum was added to the endotoxin. Six animals given 1 ml. of typhoid vaccine diluted in 20 ml. of distilled water had high fever, with a mean fever index of 150, varying between 113 and 191.

These findings with pyrexal and typhoid vaccine raised the possibility that in the presence of serum, all bacterial endotoxins are inactivated by relatively mild heating.

That the reaction is dependent upon the amount of pyrogen admixed with serum was shown by testing these six dogs with a vaccine prepared from *Salmonella typhosa* (strain Felix-Ty2). This vaccine contained approximately 20 times the number of cells that were present in Army vaccine (V-58) and gave rise to marked fevers in the animals. Heating in the presence of water and serum did not affect the magnitude of these febrile responses (Figs. 5C, 5D, 6).

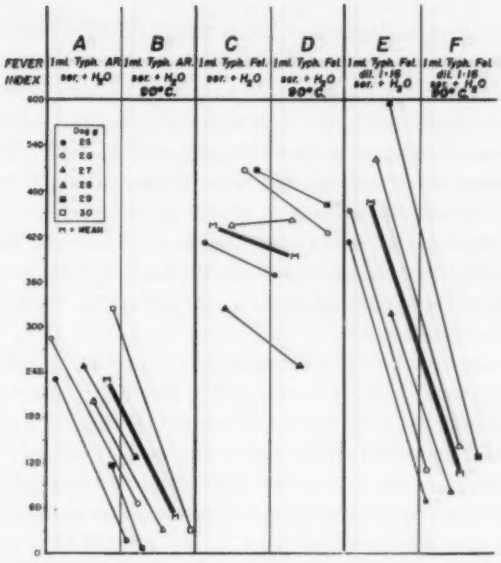

FIG. 5. Fever indices of 6 dogs given various mixtures of typhoid vaccine, serum and water in the heated and unheated state.

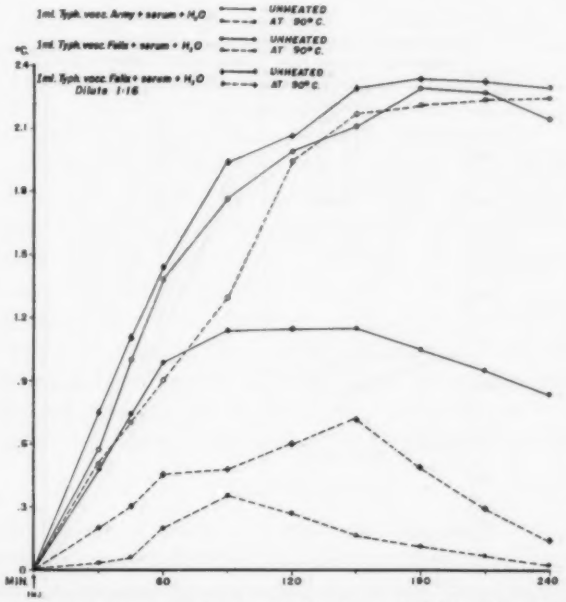

FIG. 6. Temperature responses in 6 animals after administration of several typhoid vaccines in serum, heated and unheated.

When diluted 1:16 to approximate the potency of the Army vaccine (V-58), (as measured by optical density on a Bausch and Lomb spectrophotometer) 1.0 ml. of unheated Felix vaccine still gave rise to high fever. However, in contrast to the results with the concentrated vaccine, heating the dilute serum-water-pyrogen mixture reduced its pyrogenic activity. (Figs. 5E, 5F, 6).

The fevers observed in test animals were similar after 1.0 ml. of undiluted vaccine (Felix) heated and unheated, or 1.0 ml. of 1:16 vaccine. (Figs. 5C, 5D, 5E). This implies that a maximal febrile response had been attained in these animals, and it is probable that even had heating destroyed the pyrogenic activity of most of the undiluted vaccine, the difference would not have been detectable in this test system.

C. *E. coli vaccine.* 1.0 ml. of a formalin-killed vaccine of this organism (referred to in Figs. 7 and 8 as "*E. coli* broth") resulted in fever of considerable magnitude when injected with water and serum. Heating this mixture at 90°C. for 30 minutes did not affect these results appreciably. (Figs. 7A, 7B, and 8).

In order to evaluate the possibility that failure of heating to destroy the fever-producing capacity of this preparation was due to the broth medium, a heat-killed vaccine was prepared from *E. coli* using 0.85 per cent NaCl and

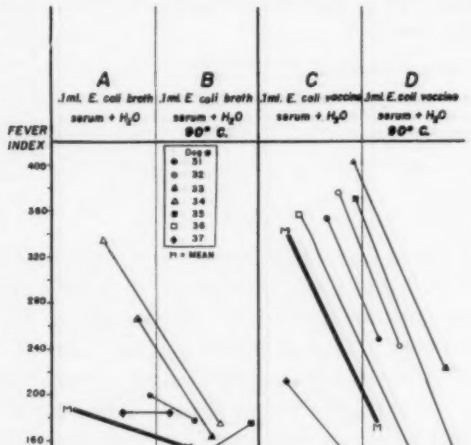

FIG. 7. The thermogenic effect of intravenous injection of unheated and heated *E. coli* vaccine-serum-water mixture in 7 dogs.

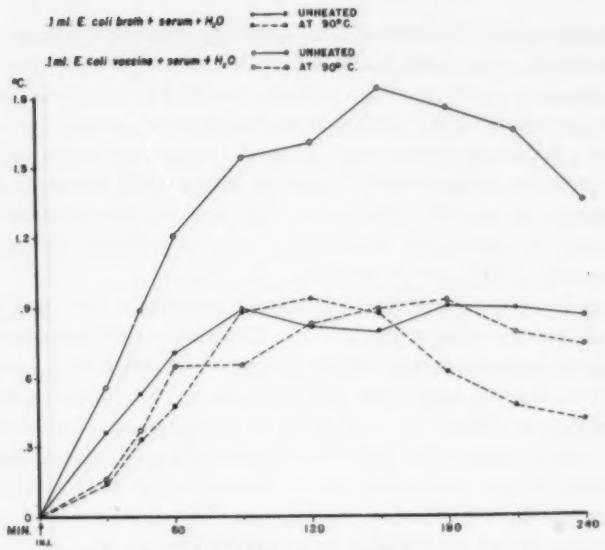

FIG. 8. Fever records of 7 animals injected with two different *E. coli* vaccines mixed with serum and water, and exposed to 90°C. for 30 minutes.

0.5 per cent phenol as a suspending medium (referred to as "*E. coli* vaccine" in Figs. 7 and 8). A mixture of 10 ml. of serum, 10 ml. of distilled water and 0.1 ml. of this vaccine (containing 3×10^8 cells) was a potent pyrogenic stimulus in test animals (Fig. 7C). Five animals given 0.1 ml. of the vaccine diluted in 20 ml. of distilled water alone, heated at 90°C. for 30 minutes, reacted with fever indices of 376, 297, 511, 414, and 332, a mean of 363, comparable to the response to the same amount of vaccine in serum in the unheated state (Fig. 7C). Although heating the vaccine in the presence of serum and distilled water did not entirely eliminate the febrile response of test animals, a consistent reduction in fever was noted (Fig. 7D).

In general, then, the results obtained with pyrexal, typhoid vaccine, and *E. coli* vaccine indicate that in the *presence of serum*, bacterial endotoxins can be completely inactivated by heating at 90°C. for 30 minutes when the concentration of these substances is relatively low. More concentrated pyrogens retain the ability to produce some fever in test animals after heating.

DISCUSSION

The presence in rabbit tissues of substances capable of inducing fever in test animals of the same species has been demonstrated using extracts of polymorphonuclear leukocytes, supernatant fluids from sterile peritoneal exudates, and extracts of localized inflammatory lesions (4, 7). Although the leukocyte

has been thought to be the common denominator governing the thermogenicity of these materials, other cells probably participate in view of the fact that peritoneal exudates from granulocytopenic rabbits are pyrogenic (8). All of these tissue pyrogens differ clearly from bacterial endotoxin in producing characteristic, relatively short, single-peaked temperature responses, ability to produce fever in animals made tolerant to bacterial pyrogen, failure to induce tolerance by repeated injections, and the lack of potentiation of the febrile response by thorotrast. In addition, all of these materials are inactivated by heating at 90°C. for 30 minutes.

Atkins and Wood have described a pyrogenic material in the blood of rabbits given typhoid vaccine intravenously (1, 2). This finding has been confirmed in dogs and this endogenous serum pyrogen, as has been mentioned, is characterized by certain definite properties which enable it to be distinguished from bacterial endotoxin. These are: (a) a short, monophasic fever in recipient animals, (b) ability to produce fever in animals tolerant to bacterial pyrogen, and (c) inability to produce resistance by repeated administration (3). On the basis of these similarities between endogenous serum pyrogen and leukocyte-tissue pyrogens, Wood and Atkins have suggested that the serum pyrogen arises from tissues damaged by the injected bacterial toxin, and have emphasized the role of injury to polymorphonuclear leukocytes.

Heretofore, attempts to test heat stability of pyrogenic substances in serum have been unsuccessful. However, in the present investigations, the procedure of adding distilled water prevented coagulation by heat, and the use of the dog rather than the rabbit circumvented some of the febrile reactions or sudden deaths which are frequent when slightly particulate suspensions are administered intravenously to this animal (3). These studies indicate that endogenous serum pyrogen loses its fever-promoting property after exposure to heat at 90°C. for 30 minutes. This phenomenon appears to be independent of the type of bacterial endotoxin used to produce fever. Change in ionic strength consequent to the addition of distilled water alone did not modify the thermogenic property of endogenous pyrogen.[6] Therefore, in terms of its ability to withstand heating, the 120 minute endogenous serum pyrogen was found to be similar to pyrogen derived from other tissues.

Specific interpretation of these findings is complicated, however, by the observation that exogenous pyrogens lose their thermogenicity when heated at 90°C. in the presence of serum. This could be taken to support the idea of Grant (9) that endogenous pyrogen is not a product of injured tissue, generically distinct from the originally injected endotoxin, but rather represents

[6] Endotoxins added to serum which had been heated previously did not lose their ability to produce fever, indicating that bacterial pyrogen as well as serum had to be exposed to heat for inactivation to occur.

bacterial endotoxin which has been modified by plasma components, perhaps gamma globulin (10), to become the so-called endogenous serum pyrogen. Inactivation by heat is clearly dependent on the presence of serum and, in the present studies, relatively large amounts of the same typhoid vaccine used by Atkins and Wood to stimulate the appearance of endogenous pyrogen in rabbits were invariably inactivated by exposure to 90°C. in a serum medium. If the effect of heating alone is considered, it is entirely possible that the ability of 120 minute serum to cause fever is the result of the presence in it of bacterial endotoxin in concentrations sufficiently low to be demonstrably heat-labile. This possibility is in accord with the fact that endogenous serum pyrogen is a relatively weak thermogenic agent. On the other hand, there is much to indicate that the pyrogen appearing in serum consequent to injection of endotoxin is a distinct new substance. Further experimental data are needed to clarify the relationship of these pyrogens and, hopefully, to establish a causal relationship of any of these substances to the fever of infection, hypersensitivity or inflammation.

SUMMARY AND CONCLUSION

Endogenous, "120 minute serum" pyrogen, was found to lose its ability to produce fever in dogs after heating at 90°C. for 30 minutes. Similar results were obtained when small amounts of exogenous bacterial pyrogens were heated in the presence of normal serum. Although endogenous serum pyrogen is qualitatively similar to previously described tissue pyrogens in its susceptibility to heat, this fact does not eliminate the possibility that endogenous pyrogen is bacterial endotoxin modified by the tissues of the host.

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ATRIO-VENTRICULAR DEFECT OF MEMBRANOUS SEPTUM

Left Ventricular-Right Atrial Communication with Malformed Mitral Valve Simulating Aortic Stenosis. Report of a Case

CHARLOTTE FERENCZ

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Congenital communications between the left ventricle and the right atrium, which have been described occasionally during the last 100 years (1–7) have been considered curiosities among malformations of the heart. The unexpected finding of this condition in the course of corrective cardiac surgery has stimulated interest in this malformation and has emphasized the need of clinical diagnosis, or at least suspicion, of such a defect. The variability in the anatomic alterations associated with this malformation suggests that we are not dealing with an easily recognizable syndrome. A communication between the left ventricle and the right atrium represents a malformation involving a very important area of the heart: the upper ventricular septum, the aortic outflow tract, and the primordia of the atrioventricular valves. The resulting clinical picture will be determined by the relative severity of the deformities in each of these structures.

The complexity of both the malformation and the clinical manifestations are illustrated in the following case:

M. T. HLH. No. B-21845. This 26 month old white female was known to have heart disease since birth. She was born at another hospital after an uneventful pregnancy. She had an imperforate anus, a rectovaginal fistula, and was markedly cyanotic at birth. The heart was enlarged and a loud systolic murmur was heard. During the first 12 hours of life she was thought to be in cardiac failure and was digitalized with improvement. The cyanosis disappeared within 24 hours and was never noted again. At 12 days of age a colostomy was performed. After the first month of life she was improved, and at the age of three months digitalis was discontinued, but was resumed again at 23 months of age. Her development was slow, her appetite poor, and she tired easily.

Physical examination revealed a poorly developed, thin and irritable child weighing 17.5 pounds. There was no cyanosis and no evidence of cardiac failure. The peripheral pulses were easily felt and equal in all extremities. The blood pressure was difficult to obtain but was recorded as 98/80 mm. Hg in the arms. The chest showed a pigeon breast deformity. The heart was grossly enlarged. A well-marked systolic thrill was palpable over the precordium. Murmurs were present in all phases of the cardiac cycle. A loud harsh systolic murmur was

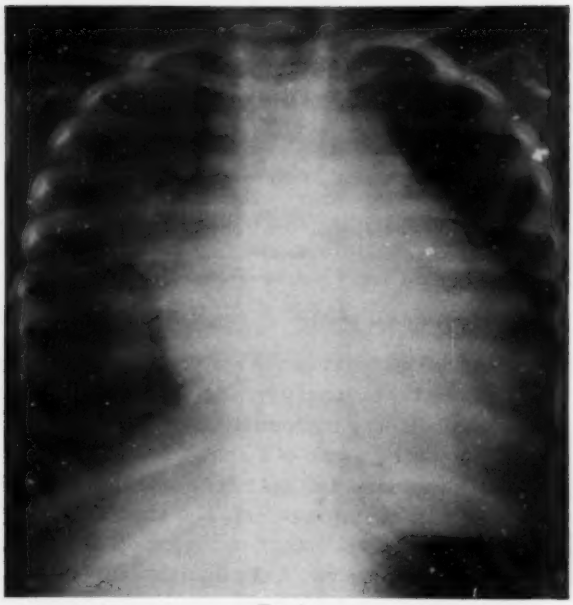

FIG. 1a

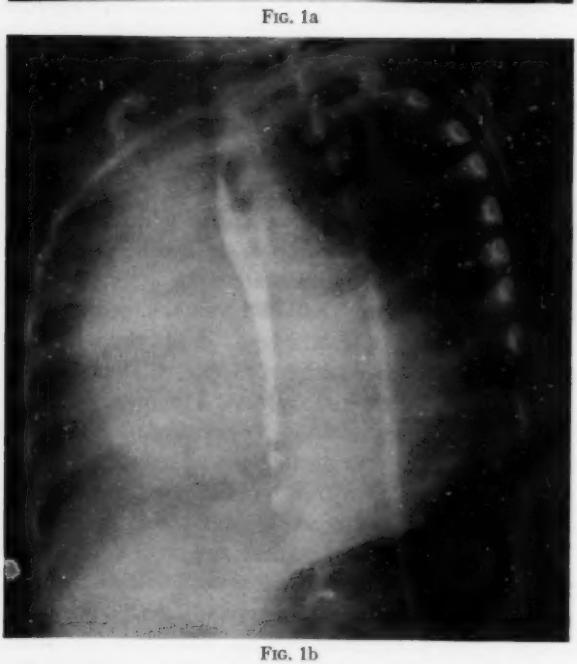

FIG. 1b

FIG. 1. Roentgenograms of chest. a. PA view, showing marked cardiac enlargement, prominent main pulmonary artery and diffuse increase of the hilar markings. b. LAO view showing huge left ventricle. c. RAO view showing enlarged left atrium projecting posteriorly.

heard at the base at both borders of the sternum. At the lower left sternal border, the systolic murmur was more blowing in character and was transmitted to the axilla and to the back. There was a rumbling diastolic murmur at the apex. Another, more harsh, diastolic murmur, not decrescendo, was heard in the 4th intercostal space a short distance away from the left sternal border. The pulmonic second sound was accentuated, the aortic second sound was barely audible.

The heart was markedly enlarged on fluoroscopy (Fig. 1a). The main pulmonary artery segment was prominent. Hilar vascular markings were diffusely increased, but showed no abnormal intrinsic pulsations. Both ventricles appeared to be enlarged, the left especially, projecting far posteriorly in the LAO view (Fig. 1b). A pulsatile mass was noted extending into the right lung field just below the hilum. In the RAO view (Fig. 1c), this mass, believed to be the left atrium, formed the posterior border of the cardiac shadow. Enlargement of the left atrium was also indicated by the course of the barium filled esophagus, which deviated to the right and posteriorly. The extent of this deviation varied with the phase of respiration and the amount of barium in the esophagus.

Electrocardiogram (Fig. 2) showed left axis deviation and a pattern of marked left ventricular hypertrophy in the unipolar precordial leads. The T-waves were inverted in all precordial leads. The P-waves were broad and notched in lead 1, and the P-R interval was prolonged. It is of interest that a

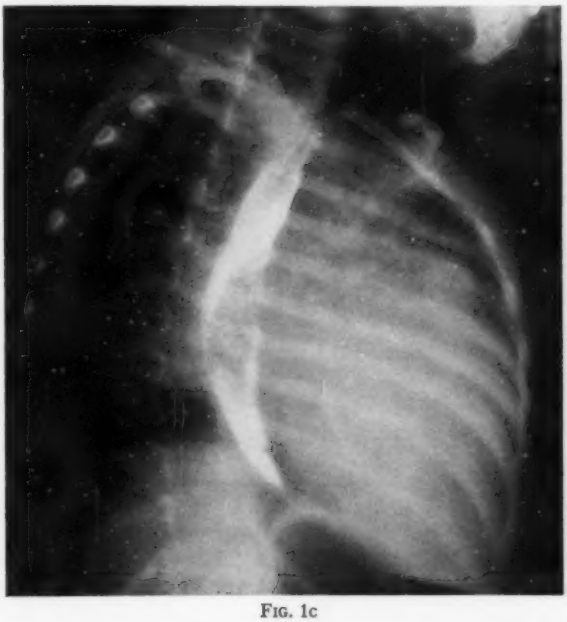

FIG. 1c

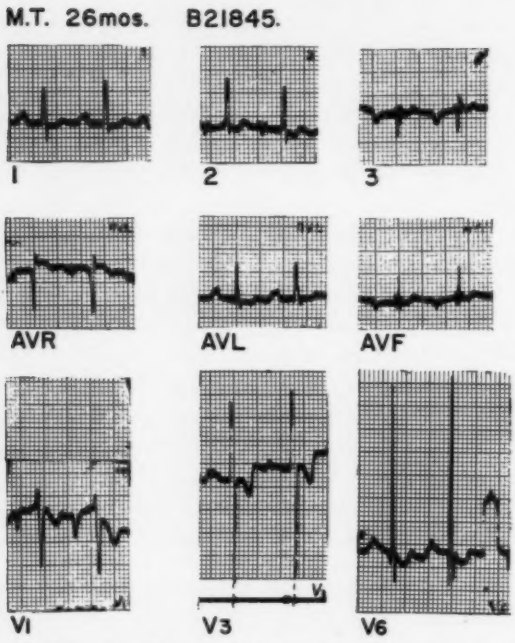

FIG. 2. Electrocardiogram of M. T. taken at 26 months of age.

TABLE I

Results of Cardiac Catheterization

Catheter position	O_2 vol %	Pressures mm. Hg
Superior vena cava	7.0	
Inferior vena cava	7.9	
Right atrium—high	7.2	
—mid	7.1	
—low	7.4	
Right ventricle—inflow	7.4	
—mid	7.4	40/2
—outflow	8.1	
Main pulmonary artery	7.6	43/35
Right pulmonary artery	6.8	
Right pulmonary—wedge	13.4	18 mean
Left ventricle		80+/21 approximately
Femoral artery	12.4 (91%)	77/45
Capacity	13.64	

tracing taken at two weeks of age showed some, but not striking, evidence of left ventricular hypertrophy.

Cardiac catheterization (Table I) revealed the following findings: There was moderate right ventricular and pulmonary hypertension and the pulmonary

wedge pressure was also elevated. During a pressure recording in the right ventricle, the catheter tip suddenly entered an area from which a much higher pressure, far exceeding the sensitivity range of the gauge used, was recorded. The catheter slipped out of this position before an accurate pressure tracing or a sample could be obtained. It was believed that the catheter passed through a septal defect from the right to the left ventricle. However, there was no other evidence of a left to right shunt either at this site or elsewhere in the right side of the heart or in the pulmonary artery.

Angiocardiography revealed an essentially normal course of the circulation without evidence of shunts. The right side of the heart was dilated and the pulmonary artery was large (Fig. 3). Dye accumulated in a greatly enlarged left atrium which extended into the right lung field in the position of the pulsatile mass noted on fluoroscopy. The left auricular appendage was prominent (Fig. 4). The left ventricle was huge. Dye lingered in the left side of the heart and emptied slowly into the aorta which was of average size, arched to the left, and branched normally.

A diagnosis was made of aortic stenosis, mitral incompetence and possibly mitral stenosis. In view of the tremendous cardiac enlargement an attempt to relieve the aortic stenosis appeared indicated.

Operation was performed by Dr. Henry T. Bahnson. When the pericardium was opened a thrill was palpated over the ascending aorta and at the base of the heart. A small opening was made at the apex of the left ventricle. A cannula

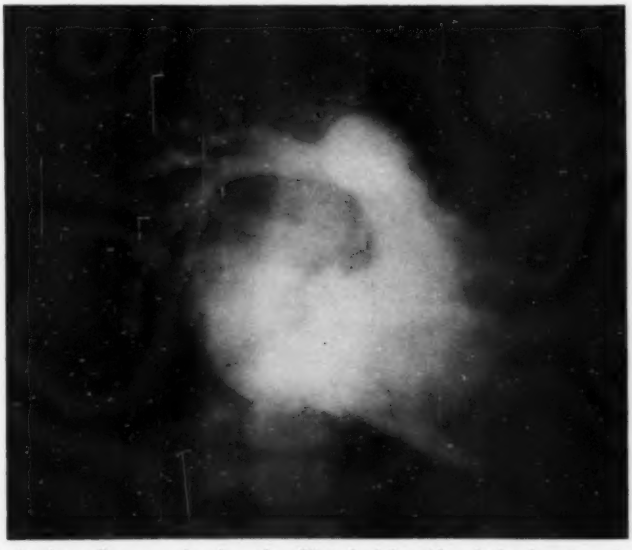

FIG. 3. Angiocardiogram showing the dilated right side of the heart and pulmonary artery. PA view.

FIG. 4. Angiocardiogram showing the large left atrium and left ventricle, dilated left atrial appendage. PA view.

was introduced and passed into the aorta. Pressure recordings established the presence of a gradient of approximately 40–50 mm. Hg across the aortic valve. A Potts dilator and subsequently a Brock dilator were introduced and passed through the aortic valve. The tearing of some tissue was noted. Following this procedure the pressure gradient between the left ventricle and aorta was practically abolished. However, the left ventricular pressure rapidly fell, cardiac arrest soon occurred and resuscitative measures were of no avail.

Post mortem examination (J.H.H. #26103) revealed a most unusual malformation of the heart. A small defect in the membranous part of the ventricular septum formed a communication between the left ventricle and the right atrium. The mitral valve was malformed and the chordae of its cleft aortic leaflet formed a dense network at the base of the aorta. Thus there was mitral incompetence and obstruction of the aortic outflow tract.

The heart was greatly enlarged, weighing 150 gms. (normal at 2 years 64 gms.). The superior and inferior venae cavae entered the right atrium normally. A left superior vena cava was present, which entered the right atrium via a dilated persistent left horn of the sinus venosus which also received the coronary sinus. The right atrium was markedly dilated. The foramen ovale was sealed. The tricuspid valve ring measured 9.0 cm. The valve leaflets were of average size and occupied their usual position, but showed nodular, gelatinous thickenings along their edges. The chordae tendineae were short and thick and the papillary muscles were poorly differentiated. The medial (septal) leaflet

was closely bound to the septum. The anterior leaflet was attached laterally to the anterior papillary muscle by short chordae tendineae, but lacked any attachment of its medial aspect to the septum thus giving rise to a free edge which projected into the pulmonary outflow tract. An oval defect, measuring 7 x 4 mm. in the fixed specimen, was located in the atrial wall just above the commissure between the septal and anterior leaflets of the tricuspid valve (Fig. 5b). Its edges were formed by thickened, gelatinous tissue. This defect com-

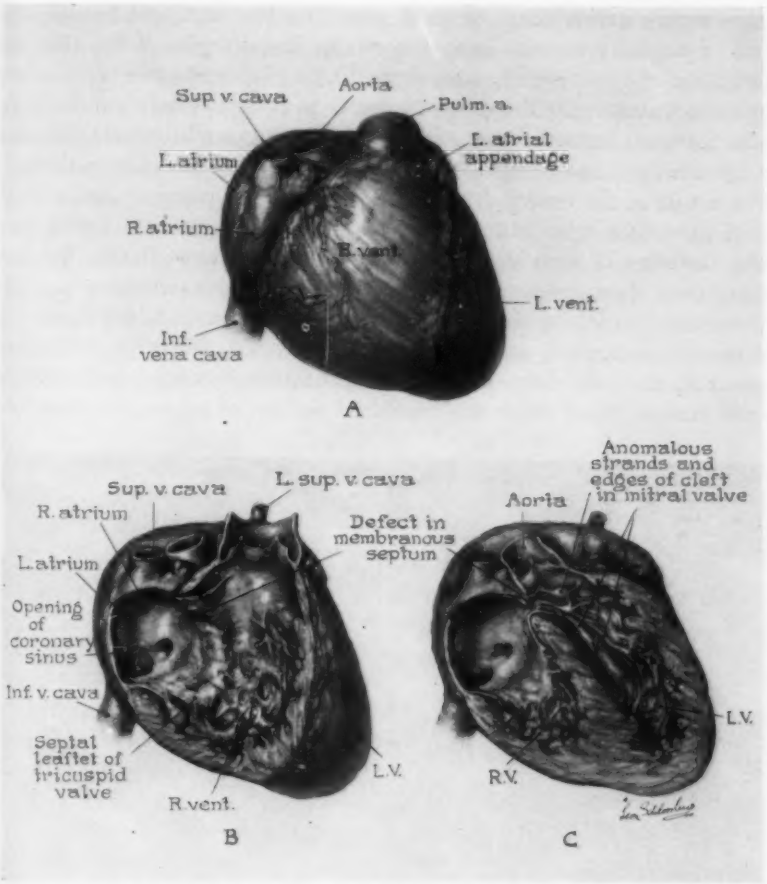

FIG. 5. a. Drawing of exterior appearance of heart for orientation. b. Drawing of specimen showing left ventricular-right atrial communication as viewed from the right atrium. c. Drawing of specimen showing malformed mitral valve, fibrous network at base of aorta and defect in the membranous ventricular septum between the left ventricle and the right atrium.

municated with the left ventricle. The right ventricle was somewhat dilated, especially the region of the pulmonary outflow tract. Its wall was markedly hypertrophied, measuring 4–7 mm. The pulmonary valve ring measured 4.5 cm. The semilunar cusps were normally formed. The main pulmonary artery was dilated and showed thickening of its wall.

The pulmonary veins entered a greatly dilated and hypertrophied left atrium. The endocardium was irregularly thickened. The mitral valve ring measured 5.5 cm. The mitral valve was grossly malformed. There was a cleft in the anterior (aortic) leaflet. Short, thick chordae attached each half to a separate group of papillary muscles located normally. The margins of the cleft were rolled under and held back by irregularly thickened short strands of endothelial tissue which attached to the ventricular surfaces of the two halves of the leaflet. These filaments formed a dense meshwork which extended across the aortic outflow tract to attach irregularly around the margins of a defect in the membranous part of the ventricular septum (Fig. 5c). The posterior leaflet of the mitral valve was essentially normal, but its chordae were thick and short. Along the edges of both leaflets there were excrescences similar to, but more marked than, those noted on the tricuspid valve. The left ventricle was dilated and markedly hypertrophied, its wall measuring 7–11 mm. in the fixed state. The mural endocardium was not abnormally thickened. The defect in the mem. branous septum communicated with the right atrium, but was largely occluded by the mass of fibers which also contained nodules of gelatinous consistency

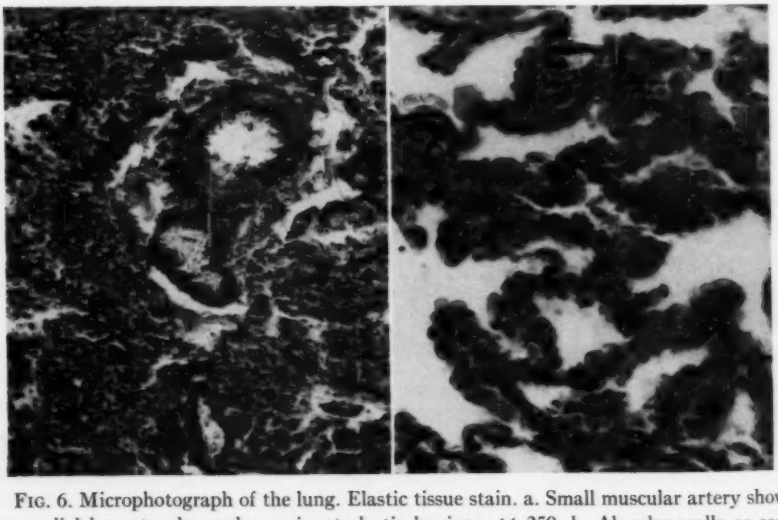

FIG. 6. Microphotograph of the lung. Elastic tissue stain. a. Small muscular artery showing medial hypertrophy and prominent elastic laminae. × 250. b. Alveolar walls as seen under high power (× 400) showing increased cellularity and compressed capillaries.

some of which measured 3 mm. in diameter. The aorta arose above these strands. Its valve ring measured 3.5 cm. It was displaced to the right, but no physiologic overriding was present because the loose connective tissue surrounding the orifice of the defect extended to the base of the aorta and thus completed the left ventricular outflow tract. This irregular membrane was in apposition with the right atrial wall. The semilunar cusps, though somewhat thickened, were well formed and the coronary arteries arose normally. The aorta showed no abnormality and the ductus arteriosus was closed.

The lungs weighed 110 gms. The left lung was collapsed. Except for a few areas of focal atelectasis, there was no gross abnormality.

Microscopic examination of the lungs (Figs. 6a & b) revealed changes comparable to those found in cases of mitral stenosis (8, 9). The alveolar walls were thickened due to cellular proliferation, interstitial edema and deposition of collagen fibres. In these cellular alveolar walls the capillaries were usually inconspicuous, but in some areas congested dilated capillaries were seen. The small arteries showed marked hypertrophy of the medial muscle and prominent elastic fibres. The thickening of the arterial walls extended to the smallest branches. Occasional slight, eccentric intimal proliferation was present. The veins were thick-walled and showed an increase in collagen and elastic fibres and some intimal proliferation. In scattered areas large numbers of heart failure cells were present in the alveoli.

DISCUSSION

The basic developmental defect responsible for this malformation concerns the closure of the interventricular foramen. The completion of the interventricular septum by the formation of its membranous part requires the union of three separate masses of connective tissue: 1, the margin of the ventricular septum, 2, the conus ridges, and 3, the atrioventricular canal cushions (10). Patten (11) has pointed out the importance of timing in the convergence of the various components designed to complete the ventricular septum and the special vulnerability of this region to developmental disturbances. Maldevelopment of the endocardial cushions may be associated with deformities of the atrioventricular valves. The septal leaflet of each valve requires for its formation the union of the dorsal and ventral portions of the atrioventricular canal cushions (10). This union fails to occur in cases of persistent ostium atrioventriculare commune in which cleavage of the septal leaflets of the mitral and tricuspid valves is a constant feature (12, 13). A cleft in the septal leaflet of the mitral valve also occurs frequently in association with persistence of the ostium primum. The two halves of the leaflet do not form an efficient valve mechanism and mitral regurgitation results. The deformity of the mitral valve observed in our patient was in every way similar to that found in such cases. The obstruction of the aortic outflow tract was merely secondary to the mal-

formation of the mitral valve. The dense network of poorly differentiated endocardial strands, attached to the halves of the cleft aortic leaflet of the mitral valve, interfered with the emptying of the left ventricle and also obstructed the passage of blood through the ventricular septal defect. The clinical picture of a severe aortic obstruction was produced. The presence of the defect itself was of no consequence. Its significance lay in the distortion of neighboring structures.

The location of the defect between the left ventricle and the right atrium is of interest. On the left ventricular side the opening was high in the membranous part of the ventricular septum, separated from the base of the aorta by a thin sheet of connective tissue which extended from the edge of the defect to the aortic valve ring. On the right atrial side the defect opened above the tricuspid valve ring in the region of the commissure between the anterior and septal leaflets. The occurrence of this communication emphasized the close relationship of right atrium, right ventricle, left ventricle and aorta at this site (Fig. 7). The upper portion of the membranous ventricular septum called the "atrioventricular part", lies in apposition with the right atrial wall. On the right atrial side, the attachment of the septal leaflet of the tricuspid valve separates

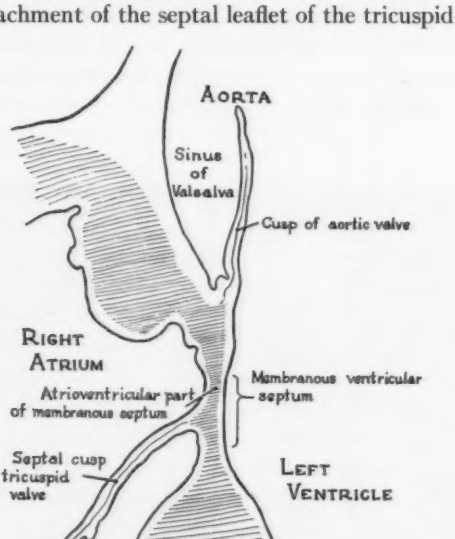

FIG. 7. Diagram based on a projection drawing of a section through the interventricular septum membranaceum of an adult human heart. Adapted from Barry A. and Patten B. M.; The structure of the adult heart. Fig. III–22: *Pathology of the Heart* by Gould, S. E. Charles C. Thomas, Springfield, Ill.

this portion from the lower, ventricular half. The usual high ventricular septal defect occurs in the lower portion and permits communication of the right and left ventricles behind the septal leaflet of the tricuspid valve. Consequently, as Edwards has shown, (12) communications between the left ventricle and the right atrium can occur in two ways: through a defect in the atrioventricular part of the membranous septum, as in our case; or through a defect in the lower part of the membranous septum associated with a defect in the tricuspid valve. In the latter instance the margins of the two defects may be adherent, so that the shunt is entirely from left ventricle into right atrium. The distinction of the two types of left ventricular-right atrial communications is of more than academic interest. The first type, the defect of the atrioventricular part of the membranous septum, is rare. It represents a malformation of the endocardial cushions and, therefore, is likely to be accompanied by cleavage of the septal leaflet of the mitral valve. Its possible occurrence should be considered in cases of congenital mitral regurgitation. In left ventricular-right atrial communications resulting from the coexistence of a double orifice of the tricuspid valve with a high ventricular septal defect defective development of the mitral valve is unlikely. The shunt may be entirely into the right atrium if the margins of the two defects are adherent, or it may be partly into the right atrium, and partly into the right ventricle if the two defects are completely or partially independent. Since surgical correction of such lesions is now feasible the recognition of the exact anatomic arrangement becomes increasingly important.

Left ventricular-right atrial communications are uncommon. Perry, Burchell, and Edwards (6) reviewed five cases found in the literature and added one of their own. These patients varied in age from 3½ months to 26 years. The clinical data available are insufficient to permit an analysis of the circulatory alterations caused by the defect. It may be expected that the clinical picture will be that of an arteriovenous shunt at the atrial level and the differential diagnosis, discussed by Edwards, (12) and by Stahlman *et al.* (7) includes defects of the interatrial septum of both the ostium primum and ostium secundum types, anomalous drainage of pulmonary veins, ventricular septal defect associated with tricuspid regurgitation, and rupture of a congenital aneurysm of a sinus of Valsalva into the right atrium. The difficulty in the differentiation of these malformations is illustrated by the two carefully studied cases reported by Stahlman *et al.* (7). It is important to realize that the problem presented by this unusual communication may be still more complex. In our patient the malformation of the mitral valve and its anomalous attachments were responsible for the physiologic alterations. The patient presented the clinical picture of aortic stenosis and mitral insufficiency. The true nature of the aortic obstruction could not have been suspected clinically. The evidence of mitral regurgitation, however, should raise the possibility of a cleft aortic leaflet of this valve.

A final consideration of left ventricular right atrial communications concerns the manner in which this defect may complicate the diagnosis and surgical correction of other malformations of the heart.

Among the cases reviewed by Perry, Burchell, and Edwards (6) associated malformations were reported by Hemsath *et al.* (4) in a patient who had a large auricular septal defect and a patent ductus, and by McCullogh and Wilbur (5) in a patient who had a large patent ductus and a "marked constriction of the aortic arch proximal to the ductus". These patients died at 2½ and 4 months of age, respectively, and represent the youngest patients reported. The earliest description of a left ventricular right atrial communication was that of Buhl quoted by Meyer, (1) in a 14 year old girl who was cyanotic from birth. She undoubtedly had an associated malformation, but the exact nature of this is not apparent from the report and the original description is not available. Dammann (14) has studied a patient in whom a left ventricular-right atrial communication was associated with a tetralogy of Fallot and a patent ductus. This was an 11 year old cyanotic girl who had a pulsating liver. The communication was of the second type, i.e. it occurred through a defect in the septal leaflet of the tricuspid valve, which was adherent to the margins of the ventricular septal defect. The right ventricle was thick-walled, but of small capacity and a diaphragm-like area of stenosis was present in the infundibulum. In this patient angiocardiogram showed evidence of a shunt from right atrium to left ventricle during atrial systole, and reversal of the shunt, i.e. a shunt from left ventricle into right atrium, during ventricular systole. Surgical relief of the infundibular stenosis was followed by severe right heart failure.

The great variation in the clinical and anatomical findings of these cases emphasizes the complicated nature of left ventricular-right atrial communications. Such defects will undoubtedly be encountered with increasing frequency as improved methods of open heart surgery lead to correction of intracardiac lesions.

A review of the developmental and anatomic features of this malformation reveals a diversity of structure and a variability of hemodynamic alterations. There is obvious need for greater awareness and more extensive study of these cases.

SUMMARY

A case report is presented of a 26 months old girl in whom a congenital communication between the left ventricle and the right atrium was present.

The clinical picture was that of aortic stenosis and mitral insufficiency. This diagnosis was supported by cardiac catheterization and angiocardiographic findings.

Postmortem examination revealed a defect in the atrioventricular part of the membranous ventricular septum. The associated cleavage of the septal

leaflet of the mitral valve resulted in mitral incompetence. A dense network of fibres attached the valve leaflets to the margins of the septal defect and caused obstruction to the aortic outflow tract.

Microscopic examination of the lungs revealed extensive alterations in the pulmonary vascular bed and alveolar walls characteristic of lesions produced by pulmonary venous obstruction.

Congenital communications between the left ventricle and the right atrium represent a malformation which affects the structures concerned in the closure of the interventricular foramen. Maldevelopment of the endocardial cushions is associated with malformations of the atrioventricular valves.

The importance of distinguishing the two types of left ventricular-right atrial communications described by Edwards, (12) is emphasized. Defects which occur above the tricuspid valve ring, are likely to be associated with malformed atrioventricular valves. Those which occur below the valve ring represent coexistence of a ventricular septal defect with a double orifice of the tricuspid valve.

The occurrence of left ventricular-right atrial communications may complicate the diagnosis and surgical correction of associated malformations. The great variability of anatomic and physiologic alterations produced by this defect is emphasized.

ACKNOWLEDGMENTS

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SPLENECTOMY IN HEMOPHILIA[1, 2]

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INTRODUCTION

It has been reported that splenectomy in three hemophilic patients resulted in appreciable clinical improvement (1, 2). In two of these instances splenectomy was performed as an elective procedure (1) and in the third because of traumatic rupture of the spleen (2). A review of these reports leaves some doubt whether all of these patients really had hemophilia, or if hemophilia were present, whether it was of classical severity. The brief case reports also imply that the splenectomies were accomplished with relative ease.

For these reasons it seems of value to document in detail, experience with splenectomy in four classical human hemophiliacs and two hemophilic dogs. The operations on the patients were performed in 1950 and 1951 in three different hospitals in Nashville. The dogs were splenectomized in the Pathology Laboratory of the University of North Carolina in 1951 and 1952. On the basis of the Nashville experience, splenectomy has received favorable comment by others in the treatment of hemophilia (3, 4). Unfortunately, the laboratory tests undertaken before and immediately after operation on the human hemophiliacs were not rigidly standardized. The present authors did not see the surviving patients until several years after operation. The splenectomies on the hemophilic dogs, on the other hand, were performed deliberately with careful preoperative and postoperative studies. The authors learned by chance of the independently originated experiments and thought it would be interesting to combine all the material on splenectomy in hemophilia into a single publication.

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I. HUMAN STUDIES

Methods and materials

The experimental methods described here apply only to the determinations carried out by the authors postoperatively. The results are recorded in the section entitled Special Laboratory Studies. Precise information is lacking on the preoperative studies recorded in the Case Reports except that usually some form of a "three-tube method" was used for the whole blood clotting time determinations.

Bleeding times were performed by the Duke and Ivy methods. The Rumpel-Leede tourniquet test was used as a measure of capillary fragility. Platelet counts were performed by the phase microscopy method of Brecher and Cronkite (5). The fibrinogen concentration of plasma was determined by the method of Ratnoff and Menzie (6). The whole blood clotting time determinations were performed by a three tube method. One ml. of blood was placed in each of three scrupulously clean pyrex test tubes (13 x 100 mm.) and the test carried out at 37°C. Only the clotting time in the third tube will be recorded in the table for the sake of brevity. With this method normal individuals have a clotting time of 20 to 30 minutes.

One-stage prothrombin times were performed using human brain thromboplastin prepared by a modification of the method of Brambel (7). Prothrombin concentration was determined by the two-stage method of Ware and Seegers (8). The test for circulating anticoagulants described by Conley, Hartmann and Morse was employed (9). An assay for antihemophilic factor was carried out by the method of Graham, Collins, Godwin and Brinkhous (10).

The thromboplastin generation test of Biggs and Macfarlane was employed to differentiate classical hemophilia from Christmas disease. The one-stage "prothrombin consumption" method of Quick and Favre-Gilly was used (11). Residual prothrombin activity in the serum was also measured by a modification of the two-stage method of Ware and Seegers (8).

Case reports

Case 1. O. L. R., (St. Thomas Hospital #15166), a 31 year old white male, was first seen at this hospital in 1947 for spontaneous hemarthroses. A life-long history of a hemorrhagic diathesis included repeated epistaxes, many spontaneous hemarthroses, and excessive bleeding following dental extractions. A brother had a similar bleeding tendency, was struck on the forehead at 12 years of age, and died several days later of undiscovered cause. There was no history of abnormal bleeding in other members of the family.

From 1947 to 1951, the patient was hospitalized three times for hemarthroses and hematuria. In February 1951, he was again admitted for spontaneous hemarthroses. The blood pressure was 128/80. Examination of the heart, lungs, and abdomen revealed no abnormalities. The spleen was not palpable. Several ecchymoses were present, and the left elbow and right knee were swollen and tender. There was moderate limitation of motion of the left wrist, right elbow, and both knees.

The urinalysis revealed normal results. Pertinent laboratory data were as follows: WBC 7,050, normal white cell differential count, RBC 4.35 million, volume of packed red cells 46 per cent, platelets 300,000, bleeding time 3 minutes, clotting time 40 minutes, and prothrombin concentration 74 per cent of normal.

The patient was readmitted in September 1951, for splenectomy and received 500 ml. of blood just prior to the procedure. He apparently withstood the operation itself well, receiving 1000 ml. of blood during the procedure. The spleen weighed 152 grams and appeared normal. Three hours after operation the blood pressure fell to 80/60, remaining at this level for

another 3 hours. He was given an additional 3000 ml. of blood. The following day the patient underwent exploratory laparotomy which revealed the peritoneal cavity to be full of blood clots. All clots were removed and gel foam soaked with thrombin was applied to the tail of the pancreas, the apparent site of bleeding.

During the next 12 days the patient received another 2000 ml. of blood. Renal shutdown was apparent on the 4th postoperative day. On the 13th day he suddenly developed massive hematemesis and expired. Autopsy revealed extensive retroperitoneal hemorrhage, hemoperitoneum of an estimated 2000 ml., acute pericarditis, and postoperative fat necrosis of the pancreas. The autopsy protocol made no mention of accessory spleens.

Case 2. B. O., (VUH #168634), a white male was first seen and hospitalized in 1948 at the age of 11 months because of a large abdominal wall hematoma. He had not been circumcised. For 4 months he had experienced numerous spontaneous ecchymoses and hematomas. In subsequent years the patient's younger brother, who had a similar clinical picture, was found to have a prolonged clotting time and a normal bleeding time and platelet count. Pertinent laboratory studies on the patient in 1948 were: WBC 12,600, normal white cell differential count, hemoglobin 6.0 grams per cent, volume of packed red cells 22 per cent, RBC 2.97 million, platelets 560,000, bleeding time 15 minutes, clotting time 90 minutes, normal prothrombin time, plasma fibrinogen 279 mg. per cent, and a negative tourniquet test.

During the following three years the patient experienced numerous spontaneous ecchymoses and prolonged bleeding following trivial injury. Thirteen hospitalizations were required for various hemorrhagic manifestations. Clotting times were variously recorded from 3 to 115 minutes.

In May 1951, he was hospitalized for the 15th time with a large thoracic wall hematoma. The blood pressure was 130/70. Examination of the heart and lungs was within normal limits. The spleen was not felt. The remainder of the physical examination was not remarkable. There was a normochromic, normocytic anemia with a volume of packed red cells of 34 per cent. The WBC and differential white cell count were normal. Platelets were 584,000. The clotting time was longer than 250 minutes. Bleeding time, prothrombin time, and plasma fibrinogen concentration were normal. The serum calcium was 10.1 mg. per cent.

Apparently operation was carried out on this young child to see if performance of splenectomy in early life, might ameliorate the future clinical course of the disease. The patient "withstood the procedure well" although he required 2000 ml. of blood during the operation. The spleen weighed 53 grams, and microscopic sections revealed an entirely normal organ.

Hematemesis and persistent bleeding from the wound complicated the postoperative course. During the first nine days 1100 ml. of blood were given and thrombin was repeatedly applied to the wound. Whole blood clotting times varied between 70 and 100 minutes, and the volume of packed red cells fluctuated between 26 and 34 per cent. He was discharged on the 28th postoperative day.

Following discharge the patient continued to experience frequent spontaneous hemorrhages necessitating many outpatient clinic visits and five hospitalizations in a two year period. Clotting times were variously recorded between 28 and 180 minutes. In May 1953, the patient died of pneumococcal meningitis.[5]

Case 3. A 30 year old white male, (Thayer VA Hospital Reg. No. 51–993), was first seen

[5] The occurrence of fatal pneumococcal meningitis is of possible interest in relationship to the recent report of increased susceptibility to infection on the part of infants or young children following splenectomy (Smith, C. H., Erlandson, M., Schulman, I., and Stern, G.: Hazard of severe infections in splenectomized infants and children. Am. J. Med., 1957, *22:* 390). Both pneumococcal etiology and meningeal localization were frequently noted in this report.

in September 1950, because of severe epistaxis. A distant maternal male relative, who migrated from England to Canada around 1700, was said to have had an hemorrhagic disorder. The patient's maternal grandfather was a known bleeder. A younger brother bled to death at age 2 years.

From early childhood the patient experienced repeated spontaneous hemarthroses, epistaxes, easy bruising, and prolonged bleeding following trivial injury. During adolescence bleeding of several days duration followed dental extractions on repeated occasions. Transfusions were required at these and other times.

The blood pressure was 140/100. Examination of the heart and lungs revealed no abnormalities. Abdominal examination was not remarkable. The spleen could not be felt. The only remarkable physical finding recorded was a large ecchymosis of the thigh. Pertinent laboratory data were as follows: urinalysis normal, WBC 5400, normal white cell differential count, RBC 5.1 million, volume of packed red cells 48 per cent, platelets 347,000, clotting time 80 minutes, bleeding time 3 minutes, normal clot retraction, and normal prothrombin time. The serum calcium was 10.2 mg. per cent.

In October 1950, a splenectomy was performed. The patient received 2000 ml. of blood, and the operative note indicated that he withstood the procedure well. The spleen weighed 260 grams. Microscopic sections revealed a normal spleen. Postoperatively the patient received only 200 ml. of blood which was given on the day the procedure was carried out. On the 3rd day he developed pulmonary atelectasis and bronchopneumonia which were successfully treated with appropriate measures. The blood pressure was stable at approximately 150/100 during the entire postoperative course. During the first two days the pulse rate fluctuated between 90 and 120 per minute, and thereafter stabilized between 90 and 100. Wound healing was delayed by the formation of a hematoma. At the time of discharge the silicone tube clotting time was recorded as approximately 3 hours.

After discharge the Lee-White clotting times were recorded as varying between 12 and 33 minutes in the Thayer VA Hospital Laboratory. In August 1953, the patient was twice hospitalized for blood transfusions because of profound anemia secondary to severe gastrointestinal hemorrhage. The patient's opinion is that he has not been improved by the operation.

Case 4. P. H., (VUH # 198433), a 41 year old white male was first seen in April 1951. He had not been circumcised. Since infancy he had experienced spontaneous hemarthroses, severe hemorrhage following dental extractions, epistaxes, and bleeding gums. The patient's brother has a similar bleeding tendency. No other relatives are known to have an hemorrhagic disorder.

The blood pressure was 140/90. A few ecchymoses were scattered over the trunk and extremities. Examination of the heart and lungs revealed no abnormalities. The spleen was not palpable, but the liver was felt 3 cm. below the right costal margin. There was slight to moderate limitation of motion of both knees and both elbows. The remainder of the physical examination was not remarkable.

The urinalysis revealed normal findings. Pertinent blood studies were as follows: WBC 7,800, normal differential white cell count, volume of packed red cells 40 per cent, hemoglobin 12 grams per cent, RBC 4.32 million, and platelets 164,000. The clotting time was 255 minutes, the bleeding time 4½ minutes, and the prothrombin time normal. A battery of blood chemistry determinations were within normal limits.

The spleen and one small accessory spleen were removed through a high left paramedian incision. The patient withstood the procedure well, receiving 500 ml. of blood during the operation. The spleen weighed 145 grams, and microscopic sections revealed a normal pattern. The first postoperative day the clotting time was 80 minutes and the blood pressure 100/60. Hematemesis and renal shutdown developed on the 3rd day. Acute gastric dilatation

occurred on the 8th postoperative day. The blood pressure promptly fell to 90/60 but was corrected with the use of neosynephrine and whole blood transfusions. Fresh ecchymoses appeared on the trunk and legs on the 21st day. The clotting time fluctuated between 25 and 145 minutes. During the first three postoperative weeks the patient received a total of 7350 ml. of whole blood.

He was again hospitalized in October 1951, for a trial of ACTH therapy. The clotting time on admission was 105 minutes and nine days of therapy with ACTH in amounts varying from 20 to 80 units per day failed to alter the clotting time appreciably. Since that time two additional hospitalizations have been necessary for persistent hematuria.

Before operation the patient experienced episodes of mild spontaneous hemarthroses about twice yearly and severe attacks about once yearly. There were also frequent ecchymoses and superficial hematomas. Since operation the frequency of spontaneous skin hemorrhages and hemarthroses has remained unchanged. Before splenectomy the patient had required hospitalization for hemorrhage six times in 15 years and since operation three times in four years. The patient feels that his condition may have been improved somewhat by the splenectomy.

Special laboratory studies

In all four patients it was impossible to evaluate with precision the laboratory data recorded in the above case reports because rigidly prescribed methods were not followed. Therefore, one cannot compare preoperative laboratory data with those obtained by the present authors in their recent investigation of the two patients (cases 3 and 4) still available for study. Nevertheless, it is possible to compare the splenectomized patients with the large group of non-splenectomized hemophiliacs under our care and with hemophiliacs generally.

One fact concerning the two patients no longer available for study is clear. Some of the clotting time determinations obtained in the immediate postoperative period were at least as prolonged as those of the preoperative period.

Within the past year studies on cases 3 and 4 were performed in our laboratory by rigidly controlled methods. The following tests were within normal limits on repeated occasions: bleeding time, tourniquet test, platelet counts and morphology, one- and two-stage prothrombin tests, clot retraction, quality of clot, plasma fibrinogen concentration, and test for circulating anticoagulants. Table I shows the results of the most pertinent laboratory tests in the two patients available for our study. "Prothrombin consumption" was still markedly impaired when the blood during coagulation was exposed to an extremely large

TABLE I

Post-splenectomy Laboratory Studies on Surviving Human Hemophiliacs

Patient	Whole Blood Clotting Time	"Prothrombin Consumption"		Anti-hemophilic Factor Assay
		One-stage	Two-stage	
	min.	*per cent*	*per cent*	*per cent*
Case 3	90–170	25	0	<5
Case 4	212–300	3	0	<5
(Normal)	(20–30)	(>70)	(>70)	(>80)

area of glass surface by adding crushed glass particles after the method of Dick, Jackson and Conley (12). It is readily apparent that the coagulation defect in these two patients remains severe.

The thromboplastin generation test showed that both of these patients had classical hemophilia, not Christmas disease or one of the other hemophilioid diseases. Furthermore, the cousin of case 2 was found to have classical hemophilia, increasing greatly the probability that case 2 also had classical hemophilia. It is not possible to be certain that case 1 had classical hemophilia.

II. CANINE STUDIES

Methods and materials

Hemophilic dogs from the colony of Irish Setters in the Pathology Department of the University of North Carolina were used (13). Splenectomies were performed on a hemizygous male and a homozygous female. Careful preoperative studies and matching postoperative studies were carried out on each dog. The latter studies were not done until the surgical crisis was over, and treatment (transfusions) had been discontinued for more than one week.

Splenectomy was performed under nembutal anesthesia after preoperative preparation with a large plasma transfusion. Considerable bleeding occurred during the operations especially from tears in the splenic capsules. The splenic vascular stumps were carefully inverted several times, and the abdominal incision slowly closed in layers with meticulous hemostasis. Postoperatively the animals were maintained by frequent transfusions of whole blood or plasma at least daily until wound healing was complete. The most pernicious problem was the intermittent oozing of blood and serum from the healing abdominal wound. This was controlled by local application of Thrombin Topical (Parke Davis). One dog (5108) had a massive gastro-intestinal hemorrhage on the 10th postoperative day which was successfully treated with a large volume of whole blood.

Clotting time was determined by the two-tube modification of the method of Lee and White (14) using both plain glass and siliconed serological tubes of 8 mm. internal diameter. The end-point was solid gelation in the second tube. The clotting time of normal dogs is 6–8 minutes by this method. Prothrombin utilization was studied by the method of Buckwalter, Blythe and Brinkhous (15) using the two-stage prothrombin technic (16) modified by the addition of Factor V (17). Prothrombin content of clotting normal dog blood is usually below 10 per cent within 45 minutes after venipuncture by this technic.

Plasma AHF (antihemophilic factor) concentration was determined by both the original prothrombin utilization method (10) and the simplified clotting time assay (18). Prothrombin time of plasma was determined by the method of Quick (19). Platelet concentration was determined by a modification of Nygaard's technic (20). Ac-globulin concentration of plasma was determined by a modification of the method of Ware and Seegers (21). A normal plasma from the same normal dog in all instances, was used as a control for comparison with the hemophilic animals. The Ac-globulin level was expressed in term of per cent of the normal control.

The responsiveness of each hemophilic animal to AHF was checked before and after splenectomy by a transfusion of normal plasma (13). Also the plasma of each hemophilic animal after splenectomy was transfused into an untreated hemophilic dog to determine whether an increase in AHF level could be detected by an *in vivo* "assay" procedure.

Protocols on hemophilic dogs

Dog #5034, a hemophilic female, was born June 27, 1950, from the mating of a heterozygous female (496) and a hemophilic male (474). She was reared in the animal quarters of the Medical School, University of North Carolina, on a diet of ground dog feed (Farmers' Cooperative Exchange) supplemented with wheat germ.

In the 18½ months prior to splenectomy, she required 20 plasma transfusions totalling 804 ml., or 43.4 ml. normal plasma/month. Prior to, during, and immediately after splenectomy, she received 25 transfusions totalling 850 ml. of plasma and 1600 ml. of whole blood. She lived 35 months from the end of the postoperative period. During this time she required 57 transfusions totalling 1985 ml. of plasma and 2000 ml. of whole blood. The transfusion rate after recovery from splenectomy was therefore somewhat increased, being 57 ml. plasma plus 57 ml. of whole blood/month.

She was found dead in her cage on February 16, 1955. At autopsy, there was hemorrhage into the wall of the stomach and base of the mesentery and massive gastric dilatation. The stomach contained 4000 ml. of non-bloody fluid. No evidence of residual splenic tissue was found at autopsy.

Dog #5108, a hemophilic male, was born on February 7, 1951, from a mating between a hemophilic female (4981) and a hemophilic male (474). He was reared under the conditions described above. He lived for 26 months after splenectomy, dying on November 21, 1953 from massive, progressive hemorrhage into the muscles and subcutaneous tissues of the right leg. No evidence of residual splenic tissue was found at autopsy.

In the 7 months prior to splenectomy, he required 4 transfusions totalling 100 ml. of plasma, 14.2 ml. plasma/month. During the operative and postoperative period he was given 18 transfusions totalling 955 ml. of plasma and 1250 ml. of whole blood. This animal's post-splenectomy course is particularly interesting, because he developed a circulating anticoagulant about 7 months after splenectomy. The postoperative course has been divided arbitrarily into two periods, the preanticoagulant and postanticoagulant periods. In the 7 months prior to developing the anticoagulant, he required 19 transfusions of plasma totalling 740 ml. or about 106 ml. plasma/month. During the remaining 19 months of life, he received 140 transfusions totalling 2,030 ml. of plasma and 20,635 ml. of whole blood. He received, thus, an average of 106 ml. of plasma plus 1,086 ml. of whole blood/month after becoming "resistant" to transfused AHF.

Special laboratory studies on hemophilic dogs

The effect of splenectomy on the clotting defects of the two hemophilic dogs is shown in Tables II and III. The *in vitro* tests (Table II) show that splenectomy had no appreciable effect on clotting time, prothrombin utilization, AHF, prothrombin time, or Ac-globulin. The only significant result of splenectomy was an increase in the platelet count of dog 5034. The lack of change in Ac-globulin level should be noted especially. To our knowledge, the effect of splenectomy on the level of this factor has not been reported elsewhere.

Confirmation of the failure of splenectomy to change AHF levels in hemophilic dogs is shown by the *in vivo* experiments in Table III. In these experiments citrated plasma was prepared from the splenectomized hemophilic dogs. Two non-splenectomized hemophiliacs from our colony were transfused with

TABLE II

Clotting Tests on Hemophilic Dogs, Before and After Splenectomy

Dog	Sex	Time of Observation	Clotting Time (Min.)		% Residual Prothrombin (2-stage)					% AHF (Antihemophilic factor)		Prothrombin Time (seconds)	Platelets (per mm³)	Acglobulin (% normal)
			Glass	Silicone	Minutes After Venipuncture					Prothrombin Utilization Method	Clotting Time Method			
					0	15	30	60	120					
5108	Male	Before Splenectomy	34	—	100	100	—	82	82	<1	—	—	—	—
		After Splenectomy	39	—	100	93	89	82	67	<1	—	—	—	—
5034	Female	Before Splenectomy	27	>120	100	—	97	—	88	<7	<1	6.0	384,000	101
		After Splenectomy	28	>120	100	—	92	—	93	<4	<3	5.9	500,000	105

TABLE III

Comparison of Prothrombin Utilization in Hemophilic Dogs (5017, 5015) Before and After Receiving Plasma Transfusion (2.6 ml./kg.) from Splenectomized Hemophilic Dogs (5108, 5034)

Treatment	Recipient Hemophilic Dog	Residual Prothrombin in Recipients' Clotting Blood, %				
		Time After Venipuncture, Min.				
		0	15	30	60	120
None	5017	100	—	—	—	100
Transfusion*	5017	100	—	92	92	88
None	5015	100	122	105	79	82
Transfusion†	5015	100	104	100	93	93

* Plasma from Hemophilic male #5108, post-splenectomy.

† Plasma from Hemophilic female #5034, post-splenectomy.

plasma from the splenectomized dogs, receiving 2.6 ml./kg. body weight. In Table III are shown the prothrombin utilization rates of the non-splenectomized dogs before and 15 minutes after the transfusion. It is clearly apparent that the circulating plasma of splenectomized hemophiliacs fails to correct the fundamental hemophilic defect *in vivo*. Control studies, not shown, demonstrated that all four hemophilic dogs were capable of responding to transfusions of normal plasma. These controls exclude the possibility of a circulating anticoagulant in any of the recipient dogs at the time the tests were performed.

DISCUSSION

It is commonly recognized among students of the disease that the clinical course of hemophilia is exceedingly variable. This has been known for a long time in humans and has been found to be true also in an inbred strain of Irish setters, all of whom are transmitting the same hemophilia gene (13). Because of this variability, many therapeutic agents have been used in the past with

initial enthusiasm and subsequent disillusionment. Both *dramatic* evidence of clinical benefit and striking improvement in the coagulation defect must be present to establish the efficacy of any particular treatment for hemophilia.

The European literature contains reports dealing with three instances of splenectomy in hemophiliacs with claims of subsequent improvement in the clinical course (1, 2). That all of these cases had true hemophilia or that the disease was of classical severity cannot be ascertained. In one report the limited family study suggests that the mother had a prolonged clotting time (2), an unusual feature in hemophilia but not unusual in those hemophilioid diseases which are dominantly inherited (22). However, there is no evidence that the mother experienced hemorrhagic phenomena. This patient had had only one episode of hemarthrosis before splenectomy, following appreciable trauma. While postoperative improvement in the bleeding tendency was claimed in all three of the European cases, it is noteworthy that at least two of the patients had some manifestations of a hemorrhagic disorder postoperatively. Also, although there is little evidence that the clotting time determinations were rigidly standardized, postsplenectomy coagulation times were as long as those obtained preoperatively. None of the somewhat more sensitive methods for detecting coagulation defects such as the "prothrombin consumption" tests, were available or employed. Put baldly, these cases fail to satisfy the requirement that there be *dramatic* improvement both in the clinical picture and in the coagulation defect. The claim that clinical benefit ensued because of an improvement in "vascular factors" (1) is not readily subject to evaluation.

It is interesting that in the only reported case of splenectomy in a (presumed) hemophiliac in the United States of which we are aware, splenectomy was performed as a surgical emergency (23). Rather sketchy but clean-cut evidence in this case suggests that splenectomy did not affect the clotting defect.

In all four of our patients and the two dogs, the criteria of positive pedigrees, severe clinical bleeding (including episodes of apparently spontaneous hemarthrosis), and detailed laboratory studies of the coagulation defect firmly established the diagnosis of severe hemophilia. In none of our splenectomized subjects, human or canine, was there *dramatic* evidence of clinical improvement on long-term follow-up. Indeed, in the three patients surviving the immediate postoperative period, the subsequent course did not differ materially from the preoperative course. In the dogs the hemorrhagic diathesis was, if anything, worse after operation. In three of the four humans, there was evidence of severe postoperative bleeding and hypotension; two patients experienced renal shutdown, and one died of these complications. Furthermore, in the two patients available for subsequent study, the post splenectomy coagulation defects were as severe as any seen in a large group of other hemophiliacs investigated by the (Nashville) authors. Both of the dogs are now dead, one having developed a

strong circulating anticoagulant 7 months after operation. Thus, not only is there *no* evidence that splenectomy had a beneficial effect, but there is good evidence that it entails great risk and, therefore, is to be avoided if possible.

SUMMARY

Four hemophilic patients in Nashville underwent splenectomy in 1950-51 and two hemophilic dogs in Chapel Hill in 1951-52. Postoperative complications were slight in the dogs, but three of the humans developed severe postoperative bleeding and hypotension, and one did not survive these complications. In the three patients surviving the procedure and in both hemophilic dogs, there has been no evidence of clinical improvement. Data on transfusion requirements in the dogs, in fact, suggest that the bleeding tendency was worse postoperatively. In the two patients available for complete investigation and in the two dogs, the coagulation defects remained very severe. Splenectomy in hemophiliacs is both dangerous and a fruitless procedure.

ADDENDUM

One of us (J.B.G.) has recently studied a patient with Christmas disease who had been splenectomized some years before in another hospital under the impression that he had thrombocytopenic purpura. He still has a moderately severe hemorrhagic diathesis, and coagulation studies show definite Christmas disease. White and his associates have noted a similar case (White, S. G., Aggeler, P. M., and Glendening, M. B., Plasma Thromboplastin Component. A Hitherto Unrecognized Blood Coagulation Factor. Blood, 1953, *8*: 101.)

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ABSTRACTS OF PAPERS PRESENTED BEFORE THE MEETING OF THE JOHNS HOPKINS MEDICAL SOCIETY

February 11, 1957

PSYCHOLOGY OF PATIENTS SEEKING PLASTIC SURGERY

EUGENE MEYER AND MILTON T. EDGERTON

A group of twenty-two patients presenting themselves for elective or cosmetic plastic surgery have been studied in psychiatric interviews pre- and post-operatively. The group studied was selected chiefly on the basis of the surgeon's uncertainty as to whether expected technical success in the operative procedure would result in satisfaction to the patient. Fifteen of the twenty-two patients were operated upon at this institution. Operations requested included rhinoplasty (6), rhytidectomy (5), and operations for acne, mole, redundant skin of legs, freckles, and lipoma. Five patients requiring plastic procedures for moderate or severe deformities were also seen for various degrees of observed emotional instability (severe lymphedema of leg, deformity and malfunction of jaw, chronic leg ulcer, residual cleft palate deformity, severe X-ray burns of the perineum). Follow-up evaluation has been obtained in the great majority of operated patients,—and varies from a month to two and a half years. Results were considered good by the patient in all but two cases. In both these patients the technical results were satisfactory. In one patient (two and one-half years after operation) there was disappointment concerning failure to change a state of deeply depressed mood with paranoid ideas of reference. The second patient underwent a second operation,—a rhinoplasty—some fourteen months after rhytidectomy here and was therefore viewed as an unsatisfactory outcome in spite of subjective feelings of gratitude that persisted.

From the psychiatric standpoint, twelve patients were felt to be psychotic or seriously disturbed people. Six more were severe neurotics. In spite of this, these patients had undergone a total of 32 operations within the immediate observation period. Only one serious and two less serious post-operative disturbances occurred and these lasted for a week or less. While it may not be desirable to do elective operations on seriously disturbed people, the suggestion is made that many such people are operated upon without coming to notice as psychotic.

In twelve patients the presence of depressive affect was a prominent feature. The depressive affect and a current, to-the-patient, insolvable life-situation that aggravated or threatened to aggravate chronic depressive trends brought this group to seek surgical alterations of their body and hence their body-self as an immediate solution to feelings of helplessness and lowered self-esteem. Just how the depressive affect, in these patients, affixes itself or is commingled with the felt distortions of the body-self is not clear although there are suggestive clues in the early life-history. In some cases the immediacy of a sense of relief and pleasure following operation was further suggestive evidence of the symbolic mode of operative improvement. Consolidation of the improved mood probably depends on the patients being able to make contemplated changes in their life-situations. For the patient who can do this it would appear that the plastic surgical procedure has been a preliminary to significant and constructive change in living.

HEMORRHAGIC ENCEPHALITIS IN CHICK EMBRYOS INFECTED WITH INFLUENZA VIRUS

EDWARD W. HOOK AND ROBERT R. WAGNER

Cerebral hemorrhages occur in chick embryos infected with certain strains of influenza virus (1, 2), apparently the result of viral action on endothelium of small blood vessels. The gross lesions are striking, and are easily reproducible, and thus provide an excellent model for study of host susceptibility to viral infection. The present studies define the influence of age of the embryo, route of inoculation and prior influenza virus infection on the development of hemorrhagic brain lesions.

The amount of virus in the brain increases rapidly after intravenous infection with neurotropic influenza virus (NWS). Thirty hours after injection of 20 ID_{50} of NWS virus the titer in the brain exceeds 1 million ID_{50} and small hemorrhages appear. Most of the embryos die 36 to 48 hours after infection with intense hemorrhagic encephalitis.

The age of the embryo and the route of inoculation influence the development of brain lesions and mortality. Extensive hemorrhages occur regularly in 14 day embryos, but only moderate brain lesions develop in 12 and 16 day embryos, and no gross lesions appear in 10 day embryos. Marked cerebral hemorrhages are produced by small amounts of virus given intravenously, but larger amounts are required by the chorioallantoic or allantoic routes.

Hemorrhagic encephalitis is prevented if an allantoic infection is established 24 hours previously with the same or another influenza virus. The mortality rate and incidence of hemorrhagic encephalitis in embryos injected with normal allantoic fluid 24 hours before intravenous challenge with NWS virus (400 LD_{50}) is almost 100 per cent. Prior allantoic infection with non-neurotropic influenza virus (17,000 EID_{50}, WS strain) reduces the mortality by one-half and suppresses the development of brain lesions.

The mechanism of this protective effect is not clear. Although a small amount of virus enters the circulation after allantoic infection, it is unlikely that this is sufficient to interfere with multiplication of the challenge virus. Inhibition of viral toxic action also seems unlikely. Although bacterial endotoxins protect mice against influenza virus neurotoxicity, they do not affect influenzal hemorrhagic encephalitis in chick embryos.

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MYOCLONUS IN CATS WITH NEWCASTLE DISEASE VIRUS ENCEPHALOMYELITIS.

CHARLES N. LUTTRELL AND FREDERIK B. BANG

This study reports the occurrence of myoclonus and encephalomyelitis in cats experimentally infected with Newcastle disease virus.

The intracerebral, intracerebellar, and intracervical cord inoculation of the virulent strain of Newcastle disease virus regularly produced encephalomyelitis in adult cats. In kittens, moreover, this was achieved by intranasal and intraocular routes. They, like adult cats, developed an encephalomyelitis with convulsive phenomena. The latter were of three types emerging in stages as follows:

1. Early, rhythmical, asynchronous, sometimes synchronous flexor spasms of head, neck, trunk and extremities developed—a myoclonus varying in rate from 40–130 per minute.

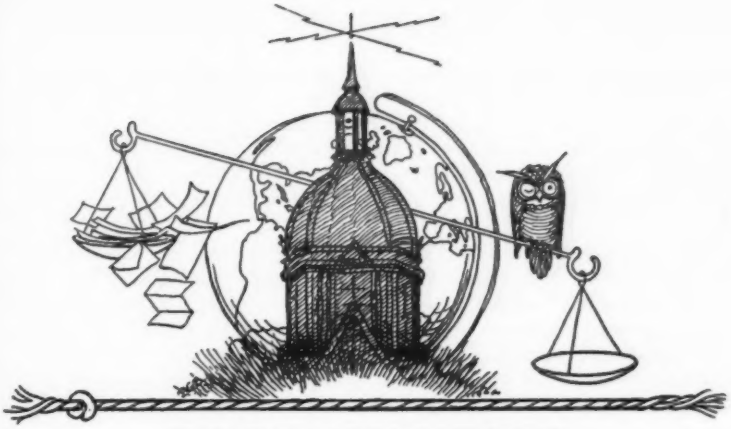
2. Later sustained extensor spasms of the upper extremities with fanning of the toes occurred.

3. Terminally in a few animals there were frank convulsions.

Electroencephalograms and electromyograms were obtained serially in seven animals. During stages 1 and 2 described above the recordings suggested that the myoclonus originated from a deep lying subcortical focus or foci.

Serial sections of brains of cats infected by the following routes: 5 intranasal, 4 intraocular, 5 intracervical cord, 2 intracerebral and 2 intracerebellar were examined and compared with two controls. The preponderant histological abnormalities were found in the brain stem and spinal gray matter.

A total of 12 brain stem and 6 high spinal transections were performed in cats with Newcastle disease virus encephalomyelitis and myoclonus. In $^{11}/_{12}$ of the brain stem and $^{5}/_{6}$ of the spinal animals the character and rate of the myoclonus was unchanged. In these cats, therefore, it seems reasonable to attribute the characteristic clinical manifestation of myoclonus to some "pathophysiological" change occurring at brain stem level or below. Moreover, it is clear that myoclonus can occur at the organizational level of the spinal cord and that suprasegmental structures are not necessary for its development or maintenance.



BOOK REVIEWS

Bladder Tumors. A Symposium. Prepared under the auspices of the American Cancer Society. 92 pp., $4.00. J. B. Lippincott Co., Philadelphia, Pa.

The difficulties which beset any attempt to assay therapeutic procedures designed to favorably alter the natural course of neoplastic diseases are all too numerous. Seemingly inconsistent studies published by numerous investigators often serve to confuse and discourage those seeking data on which to base decisions regarding patient care or on which to anchor further clinical therapeutic trials.

This symposium on bladder tumors reports the extensive experiences of the urological services at the New York Hospital and Memorial Hospital. Initially their pathologic characterization of bladder tumors is explained and the course of their untreated patients described. Subsequent chapters are devoted to assessing as best one can the results of various surgical procedures—local excision, segmental resection, simple and radical cystectomy and pelvic exenteration. Companion chapters contain accounts of a large series of permanent cutaneous ureterostomies, a review of the literature concerning secondary carcinoma of the penis and a report on the influence of sex hormones on the induction of bladder tumors in dogs by B-naphthylamine. Throughout these presentations it seemed all too apparent that the most powerful influence on a patient's course was the intrinsic nature of the neoplasm itself.

This material has been published previously in Cancer, Vol. 9, No. 3, May–June 1956.

ALBERT H. OWENS, JR.

Clinical Orthopaedics No. 8. Edited by ANTHONY F. DEPALMA. 337 pp., $7.50. J. B. Lippincott Co., Philadelphia, Pa.

Volume Eight of *Clinical Orthopaedics* is divided into three sections: (1) Chronic Hereditary Diseases and Developmental Anomalies, (2) General Orthopaedics and (3) Motorist Injuries and Motorist Safety. In the first section there are a number of very good discussions of the pathogenesis of skeletal defects, environmental factors, genetics, mutation rates, and so forth. This could hardly be considered a comprehensive review of such a vast subject, but in general, the material is very worthwhile reading. Since this material is written by many authors, there is much variation in content value and a lack of continuity. In the

second section under General Orthopaedics, the articles on haemophilic arthropathy and on prosthetic problems in children were very good. In the third section, on Motorist Injuries, the discussion of engineering aspects of fractures was very interesting. There was some question in the reviewer's mind as to whether or not the majority of the content was of special interest to the orthopaedic surgeon or just of general interest. In any case, the subject is of major importance and should come to the attention of the medical profession at large.

One problem connected with a series of this type is that there seems to be a mixture of original material with other summaries of work previously published as well as articles more or less consisting of editorial comments. It would seem better to present either in the form of monographs, exhaustive reviews of various orthopaedic subjects, or limit the material to original work. Perhaps it would be preferable to separate in some fashion the two forms of writing in order that the reader could readily distinguish between them. In general, this volume of *Clinical Orthopaedics* is well worth reading and will be a worthy addition to any orthopaedic surgeon's library.

WAYNE O. SOUTHWICK

Heart Sounds, Cardiac Pulsations, and Coronary Disease. By WILLIAM DOCK. 98 pp., $2.50. University of Kansas Press, Lawrence, Kansas.

This book is made up of the Porter Lectures (Series 21) given by Dr. Dock in 1955 at the University of Kansas. It is written in a clear, informal style, almost conversational in tone. The qualities which have won for Dr. Dock so much admiration and respect as a teacher and clinician are in evidence in this interesting and unpretentious little volume.

As the title suggests the book is divided into three parts, each dealing with a separate cardiovascular topic. The first part is concerned with cardiac pulsations and includes a discussion of local pulsations (venous, arterial and cardiac) as well as whole body pulsations (the ballistocardiogram or the "big pulse"). Dr. Dock points out that there has been a revival of interest in cardiac pulsations as a result of improvements in instruments for measuring vascular pressures, of the introduction of cardiac catheterization and of the development of ballistocardiography. Much of his research interest in recent years has been in the recording of the "big pulse" and most of this section is devoted to the nature and significance of ballistocardiograms in health and disease. Although he concedes that many unknowns remain, he presents convincing reasons for his belief that ballistocardiography can now supply important and clinically useful information about circulatory function in man.

In the second section devoted to heart sounds, the author concerns himself for the most part with the origin of normal and abnormal cardiac sounds (excluding murmurs). The various views from Harvey and Laennec onward as to the causes of heart sounds are presented including those of the opposing "muscular" and "valvular" schools. Dr. Dock provides a strong case for the valvular origin of normal heart sounds, gallop sounds and the opening snap of mitral stenosis with arguments that seem convincing.

The last section represents the author's general philosophy regarding coronary artery disease. As far as the etiology of atherosclerosis is concerned, Dr. Dock clearly and unequivocally voices the opinion that this is a preventable disease, the primary cause of which is the ingestion of excessive animal fats, particularly cholesterol. The clinical and experimental basis for this conviction is presented in a very stimulating and challenging manner. He insists that coronary disease can be blamed no longer on an act of God, overwork or the high tension of modern society when it is due to overeating, indolence and cigarette smoking.

WILLIAM R. SCARBOROUGH

The Merck Manual of Diagnosis and Therapy, 9th edition. Edited by CHARLES E. LYGHT. 1870 pp., $6.75. Merck & Co. Inc., Rahway, N. J.

The general purpose, content, and format of the ninth edition of the Merck Manual is quite similar to that of its predecessors. The initial section of this small handbook is devoted to brief remarks concerning the diagnosis and therapy of some 378 disease entities including those resulting from physical and chemical agents and venomous bites. A second section contains descriptions of the more common clinical and laboratory procedures, several tables of normal values, and a consideration of simple diet therapy. Both sections have been extensively revised in keeping with current medical progress and the expanded index appeared quite complete and easy to use.

This volume, I think, fulfills its stated purpose well, that of providing a handy quick-reference manual to physicians and members of allied professions. It is not intended to be a skeletonized text-book of medicine nor does it contain critical comment in its various expositions.

ALBERT H. OWENS, JR.

Diabetes Mellitus. Handbook for Physicians. By HOWARD F. ROOT and PRISCILLA WHITE. 346 pp., $7.00. Landsberger Medical Books. Distributed solely by The Blakiston Division of the McGraw-Hill Book Co., New York, N. Y.

The physicians of the Joslin Clinic have for many years been pre-eminent in the management and treatment of diabetes mellitus. Doctors Root and White are co-authors with Dr. Joslin in his textbook, *Treatment of Diabetes*, which has become a standard reference on this subject. This new book concentrates on the practical aspects of diabetic care and presents the views of these workers in an easily readable and quickly accessible manner. The book, though primarily designed for the practicing physician, should also be of great usefulness to the student wishing to acquire a sound approach to this subject without the encumbrance of statistical and theoretical data found in the larger volume.

The initial chapters of the book are devoted to the routine management of the diet and insulin treatment in diabetes. The remainder of the book describes the management of diabetic complications and the special problems faced in diabetics during childhood, surgery and pregnancy. Dr. White describes the care of the diabetic during pregnancy, including the use of progesterone in this condition as advocated by her. In a book of this size it is difficult to present all the evidence on so controversial a point: since in the opinion of many this form of treatment is still an experimental approach to the problem it would perhaps have been better to refer to it less dogmatically. Otherwise, the book is entirely excellent—maintaining the high standard that is expected from these workers.

JOHN A. WEAVER

Diseases of the Breast. By C. D. HAAGENSEN. 751 pp., $16.00. W. B. Saunders Co., Philadelphia, Pa.

The author of this book has devoted his professional life to the study and treatment of diseases of the breast. The book is a masterful exposition of his own work, together with his interpretations of the work of others in this field. It is beautifully printed and illustrated, and should be used as a reference work and guide by all physicians and surgeons. In the opinion of the reviewer, the methods of treating carcinoma of the breast, as advocated by Dr. Haagensen, are correct and his approach to the various methods of palliating incurable cancer is entirely reasonable and based on sound judgment.

EDWARD S. STAFFORD

BOOKS RECEIVED FOR REVIEW

Clinical Use of Radioisotopes. By WILLIAM H. BEIERWALTES, PHILIP C. JOHNSON and ARTHUR J. SOLARI. 456 pp., $11.50. W. B. Saunders Co., Philadelphia, Pa.

Pediatric Cardiology. By ALEXANDER S. NADAS. 587 pp., $12.00. W. B. Saunders Co., Philadelphia, Pa.

The Physician-Writer's Book—Tricks of the Trade of Medical Writing. By RICHARD M. HEWITT. 415 pp., $9.00. W. B. Saunders Co., Philadelphia, Pa.

The Physiology of Nerve Cells. By JOHN C. ECCLES. 270 pp., $5.75. The Johns Hopkins Press, Baltimore, Md.

Proceedings of the Third National Cancer Conference, Detroit, Michigan, June 4–6, 1956. Sponsored by American Cancer Society, Inc. and National Cancer Institute, U. S. Public Health Service. 961 pp., $9.00. J. B. Lippincott Co., Philadelphia, Pa.

Soybeans for Health, Longevity, and Economy. By PHILIP S. CHEN with the assistance of HELEN D. CHEN. 241 pp., $3.00. The Chemical Elements, South Lancaster, Mass.